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Survival analysis of transplant-eligible newly-diagnosed multiple myeloma patients harboring t(4;14), t(14;16), and/or del(17p) in the real-world setting

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ABSTRACT

Cytogenetic abnormalities (CA) such as t(4;14), t(14;16), and del(17p), are associated with a poor prognosis in Multiple Myeloma (MM) patients. However, there is scarce information regarding the Latin-American population. This study aims to analyze the impact of t(4;14), t(14;16), and del(17p) on the progression-free survival (PFS) and overall survival (OS) of transplant-eligible newly-diagnosed MM (NDMM) patients in Latin America. Retrospective survival analysis based on the Grupo de Estudio Latinoamericano de MM (GELAMM) registry, including all adult patients with NDMM harboring CA t(4;14), t(14;16), and/or del(17p). Fifty-nine patients were included; the median age was 57 years, 55.9% males, 22% ISS-I, 25.4% ISS-II, and

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47.5% ISS-III. The majority (89.8%) had one alteration, whereas 10.2% had del(17p) and t(4;14). The frequencies of CA were del(17p) in 61.0%, t(4;14) in 25.4%, and t(14;16) in 3,4%. Autologous stem cell transplantation was performed in 36 cases, 20 patients did not use this consolidative strategy, and this data was missed in three cases.
Five-year OS for the entire cohort was 60.8% and 5-year PFS was 28.1%. Bortezomib-based induction regimen (BBR) (p=0.029), consolidation with ASCT (p<0.001), and maintenance therapy (p=0.004) were associated with an improved 5-year OS. In the multivariate analysis, ASCT was the only variable with a positive impact on OS (HR 0.11, 95% CI 0.033 to 0.34, p<0.001). The median PFS presented a non-statistically significant benefit in BBR, ASCT, and maintenance therapy groups. BBR induction, ASCT, and maintenance therapy were associated with improved OS in high-risk NDMM patients.

ARTICLE INFO

Keywords: Chromosome aberrations; Multiple myeloma; Survival; Hematopoietic stem cell transplantation

Introduction

Multiple myeloma (MM) represents 10% of all hematopoietic neoplasms and is the second most frequent hematologic cancer.[1] Cytogenetic abnormalities are observed throughout the course of the disease from monoclonal gammopathy of undetermined significance (MGUS) to smoldering MM and active MM, with an impact on the clinical presentation and the risk of progression.[2,3] Conventional cytogenetics reveals abnormal karyotypes in 20-30% of MM, mainly in patients with proliferative forms of the disease.[3,4] Molecular cytogenetics studies have demonstrated that interphase fluorescence in situ hybridization (iFISH) on selected CD138+ plasma cells is the most useful technique to detect chromosomal aberrations in MM.[5] Flow cytometry, immunomagnetic-bead-based plasma cell sorting or cytoplasmic immunoglobulin light chain are adequate techniques and they all increase the detection of abnormalities.[6]

Cytogenetic abnormalities such as t(4;14), t(14;16), and del(17p) are included in the revised international staging system (R-ISS) to define the high-risk MM group (R-ISS III), which is characterized by a median overall survival (OS) of 43 months, and a median progression-free survival (PFS) of 29 months.[7] The t(4;14)(p16.3;q32) involves two protein-coding genes mapped at 4p16.3, *NSD2* (*Nuclear Receptor Binding SET Domain Protein 2*) and *FGFR3* (*fibroblast growth factor receptor 3*), the t(14;16)(q32;q23) provokes que overexpression of the *c-MAF* (*MAF BZIP Transcription Factor*) oncogene (16q23.2), and del(17p) is associated with the tumor suppressor gene *TP53* (*Tumor protein P53*) loss. These cytogenetic abnormalities are expected to occur in approximately 15%, 5%, and 10% of cases, respectively.[8,9]

However, even when there is evidence of the risk attributed to this cytogenetic alteration, the cut-offs used to define high-risk myeloma are heterogeneous among prognostic scores. In addition, new genetic variables have been included as risk factors such as del1p, 1q+, or t(14;20).[7,10–12] These factors are translated into a heterogeneous definition also in clinical trials.

An adequate therapeutic approach is important to achieve the best outcomes for the affected patients. The induction followed by consolidation with high-dose melphalan and autologous stem cell transplantation (ASCT) is the standard of care for MM patients eligible for intensive therapy. In the EMN02/HO95 trial, which defined high-risk cytogenetic patients according to R-ISS, found that in patients presenting del(17p), t(4;14), or t(14;16) the use of ASCT achieved a 5-year OS of approximately 60% (HR 0.66; 95%CI 0.45-0.99; p=0.042), and 5-year PFS of 25% (HR 0.59; 95%CI 0.34-1.03; p=0.062).[13]

In Latin America, there is limited information about high-risk FISH alterations in MM.[14–16] Therefore, the aim of this study is to analyze the impact of t(4;14), t(14;16), and del(17p) in

the PFS and OS of transplant-eligible newly-diagnosed MM (NDMM) patients from the Grupo de Estudio Latinoamericano de MM (GELAMM) registry.

Patients and methods

Design and patients

This is a retrospective survival analysis based on the GELAMM registry, including adult transplant-eligible MM patients diagnosed between 2010 and 2018, harboring one or more high-risk primary cytogenetic abnormalities: t(4;14), t(14;16), and/or del(17p). We collected clinical and laboratory data at diagnosis, data on treatment regimens, and treatment responses. The staging was performed in accordance with the International Staging System (ISS).

We did not include the evaluation of circulating plasma cells in the analysis nor measurable residual disease (MRD).

OS was defined as the interval of time from the date of diagnosis until death or last control. PFS was defined as the time from the date of diagnosis until relapse or death by any other cause.

Statistics

We used Statistical Package for Social Sciences (SPSS) v.25 and R for statistical analysis.

Descriptive statistics included quantitative and qualitative variables; quantitative variables were represented with median and interquartile ranges, with the normality of distribution determined by the Kolmogorov-Smirnov test. Qualitative nominal or ordinal variables were represented as percentages or proportions.

To compare quantitative variables, we used nonparametric methods (Mann-Whitney U or Kruskal-Wallis H). The comparison of proportions was performed with the chi-square test.

Survival was analyzed through the Kaplan-Meier model (Log-rank test); p values were considered statistically significant when < 0.05 and presented along with confidence intervals (CI). For assessing the risk association of death, hazard ratios (HR) were used. Multivariate analysis was conducted using the Cox regression model.

Ethics

The development of the GELAMM registry and the retrospective collection of the data analyzed was approved by the Ethics committees of all participating institutions. Absolute confidentiality was guaranteed during the analysis and publishing of the results as the participating hematologists in the registry send the information of each patient keeping anonymity and avoiding the use of any information that allows the identification of the patients in both, the analytic and manuscript writing phases.

Results

A retrospective analysis of the GELAMM database was done. Participating countries were Argentina, Chile, Colombia, México, and Uruguay and the data were collected from 2010 to 2018. Of 1293 NDMM included in the database, 410 had iFISH results, of whom 59 (14.39%) had one or more high-risk cytogenetic aberrations, which are the subject of this analysis. The median age was 57 years (IQR 10), and 55.9% were males. The frequency according to ISS risk groups (n=56) was ISS-I 22%, ISS-II 25.4%, ISS-III 47.5%, and missing in 5.1%. The median hemoglobin level was 10.5 g/dl (IQR 3.4), the median creatinine level was 1.2 mg/dl (IQR 1.3), and the median serum

Table 1
Characteristics of the patients included

	Total		t(4,14)		t(14,16)		del17p	
	n	%	n	%	n	%	n	%
Patients included	59	100.0	21	100.0	2	100.0	42	100.0
Sex								
Males	33	55.9	12	57.1	2	100.0	22	52.4
Females	26	44.1	9	42.9	0	0.0	20	47.6
Number of cytogenetic alterations								
One	53	89.8	15	71.4	2	100.0	36	85.7
Two	6	10.2	6	28.6	0	0.0	6	14.3
ISS group								
ISS-I	13	22.0	3	14.3	1	50.0	10	23.8
ISS-II	15	25.4	8	38.1	0	0.0	10	23.8
ISSS-III	28	47.5	10	47.6	1	50.0	19	45.2
Not specified	3	5.1	0	0.0	0	0.0	3	7.1
Induction therapy								
BBR	46	78.0	14	66.6	1	50.0	34	80.9
Non-BBR	12	20.3	6	28.6	1	50.0	8	19.1
Not specified	1	1.7	1	4.8	0	0.0	0	0.0
ASCT								
Yes	36	61.0	12	57.1	1	50.0	27	64.2
No	20	33.9	8	38.1	1	50.0	13	31.0
Not specified	3	5.1	1	4.8	0	0.0	2	4.8
Maintenance								
Yes	23	39.0	7	33.3	1	50.0	18	42.9
No	23	39.0	9	42.9	1	50.0	15	35.7
Not specified	13	22.0	5	23.8	0	0.0	9	21.4
Tumoral burden								
Lytic bone lesions	38	64.4	14	66.7	0	0.0	27	64.3
Hemoglobin (median, IQR)	10.5	3.4	9.9	2.4	11,0	2.5	11.0	2.8
Creatinine (median, IQR)	1.2	1.3	1.1	1.3	1.2	0.6	1.1	1.1
Serum Calcium (median, IQR)	9.8	2.1	10.3	2.3	9,8	1.1	9.7	1.7

CA, cytogenetical alteration; ISS, International Staging System; M, median; IQR, interquartile range; n, number; *Including patients with simultaneous del17p; **Including patients with simultaneous t(4;14).

calcium level was 9.8 mg/dl (IQR 2.1). Lytic bone lesions were reported in 63.3% of cases. Six patients required renal replacement therapy at diagnosis. Fifteen patients (15/19) presented either bone plasmacytoma or extramedullary plasmacytoma However, this data was missing in 40 patients, The status of lactate dehydrogenase (LDH) was reported in 36 cases, and from them, 11 had high levels of LDH.

The clinical and cytogenetic characteristics of patients are detailed in Table 1.

Regarding the cytogenetic abnormalities, 89.8% had one alteration of whom 61.0% had del(17p), 25.4% had t(4;14), and 3.4% had t(14;16). The remaining 10.2% presented the combination of del(17p) and t(4;14).

Treatment

Induction treatment was VCD (Bortezomib, cyclophosphamide, and dexamethasone) in 31 patients (52.5%), VTD (Bortezomib, thalidomide, and dexamethasone) in 12 (20.3%), CTD (Cyclophosphamide, thalidomide, and dexamethasone) in 8 (13.56%), VRD (Bortezomib, Lenalidomide, and dexamethasone) in 3 (5.1%), 4 TD (Thalidomide and dexamethasone) (6.8%), and 1 (1.7%) other not specified. The median number of cycles was six (IQR 2).

ASCT was done in 36 patients. Twenty patients did not receive ASCT, and in 3 cases this information is missing. No patient received tandem ASCT. The median age of the 20 patients that did not receive ASCT as consolidative therapy was 57 years (IQR 9,5).

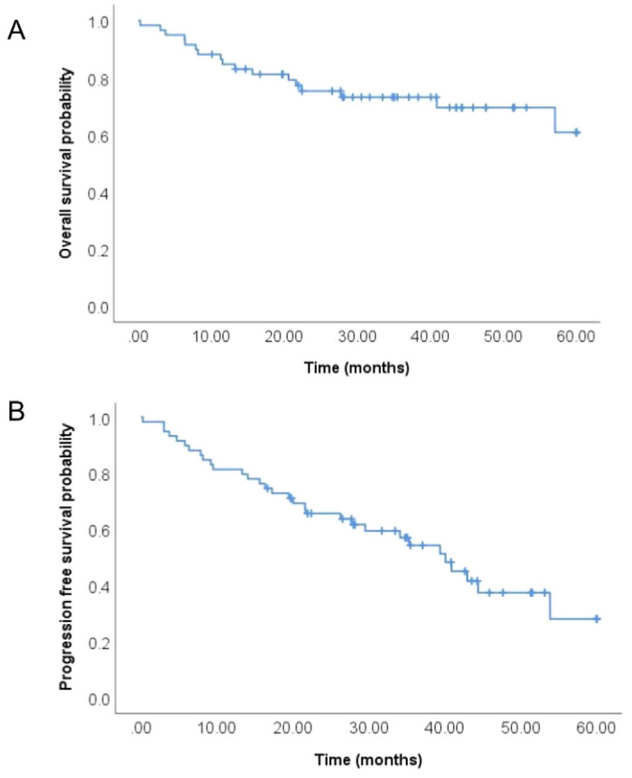

Fig. 1. Kaplan Meier survival curve for; A, Overall survival for the whole group of patients; B, Progression-free survival for the whole group of patients.

Maintenance therapy was used in 39.0% (11.9% Thalidomide, 10.16% Lenalidomide, 10.16% bortezomib, and 6.78% others). The duration of maintenance was not recorded.

Response rates

Post-induction response was reported in 22 patients, from them the rates of specific types of response were 9.1% sCR, 18.2% VGPR, 45.5% PR, 18.2% stable disease, and 9.1% progression.

After ASCT, the response was reported in all 36 cases, from them, 16.67% sRC, 22.22% RC, 30.56% VGPR, and 30.56% PR.

Survival analysis

The median follow-up was 32 months. Five-year OS for the entire cohort was 60.3% (Fig. 1A) with the median OS not reached, and the 5-year PFS was 28.1% with a median PFS of 40.1 months (Fig. 1B). No significative differences were found comparing ISS groups in OS (5-year OS, ISS-I 81.5%, ISS-II 59.1%, ISS-III 55.8%, Log-rank test p=0.60) neither PFS (5-year PFS, ISS-I 39.6%, ISS-II 32.3%, ISS-III 19.6%, Log-rank test p=0.91).

Forty-six patients received a bortezomib-based induction regimen (BBR), which was associated with a 5-year OS of 76.5%, compared to 35.0% in the non-BBR induction (n=12), with a

median OS not reached in the BBR group versus 40.9 months in the non-BBR (Log-rank test p=0.029) (Figure 2A). The 5-year PFS was 32.2% in the BBR group versus 9.7% in the non-BBR (Log-rank test p=0.058).

The use of frontline ASCT (n=36) consolidation was associated with a 5-year OS of 85.0% compared to 20.0% in the non-ASCT group (n=20). In the group receiving ASCT, the median OS was not reached, compared to 27.76 months in the non-ASCT group (Log-rank test p<0.001). (Figure 2C). The 5-year PFS was 29.1% in the ASCT group versus 20.5% in the non-ASCT (Log-rank test p=0.064).

The patients that received maintenance (n=23) therapy achieved a 5-year OS of 86.5% versus 34.3% in those not receiving maintenance (n=23) (Log-rank test, p=0.004). The 5-year PFS was 22.2% in the maintenance group versus 26% in the group without maintenance (Log-rank test p=0.055). This was independent of the drug used for maintenance.

In the multivariate analysis, ASCT was the only therapeutic variable with a positive impact on OS (HR 0.11, 95% CI 0.033 to 0.34, p<0.001).

Discussion

MM is a genetically complex disease characterized by a multistep process in which genetic alterations accumulate, endowing aggressiveness and resistance in the neoplastic plasma cell, and reduced survival.[17] In 2015, del17p, t(4;14), and t(14;16), were included in the R-ISS, defining a high-risk subgroup, with a 5-year OS rate of 40% and a 5-year PFS rate of 24%.[7]

The ideal treatment for these patients is yet to be defined. However, induction with proteasome inhibitors, tandem ASCT, and prolonged maintenance have been a survival advantage. Although the role of ASCT is being challenged by the advent of novel drugs, a recent meta-analysis of randomized controlled trials showed that upfront ASCT improves OS in high-risk NDMM patients.[18]

International recommendations highlight the importance of selecting plasma cells to obtain adequate iFISH results.[19] As reported by Cardona-Benavides, et al., using this methodology, the estimated frequency of t(4;14), and t(14;16) corresponds to 15% and 5%, of NDMM patients, respectively.[20] Del17p is expected to be present in 5% to 12%.[1] Our transplant-eligible database included 410 NDMM patients with iFISH analysis done, in which t(4;14), t(14;16), and del17p were observed in 5.12%, 0.49%, and 10.24%, respectively, which is lower than expected, probably related to the low availability of iFISH in Latin America.

In high-risk NDMM, BBR induction therapy followed by ASCT has been associated with improved outcomes. In IFM-2005-01 trial, bortezomib-dexamethasone (Vd) showed a superior response rate (≥very good partial response, 37.7% vs 15.1%) and PFS (median PFS 36.0 months vs 29.7 months, p=0.064) compared with vincristine-doxorubicin-dexamethasone (VAD) as induction before ASCT.[21] This combination improved event-free survival (EFS) (Vd median EFS 28 months vs VAD 16 months, p=0.001) and OS (Vd 4-year OS of 63% vs VAD 32%, p=0.001) for patients with t(4;14) although it did not improve outcomes in del(17p).[22] On the other hand, in the HOVON65/GMMG-HD4 study, bortezomib, doxorubicin, and dexamethasone induction, followed by ASCT and bortezomib maintenance demonstrated improving PFS (3-year PFS 27% vs 16%), and OS (3-year OS 60% vs 19%), compared with VAD, in patients with del(17p).[23] Similarly, we observed a better PFS and OS trend in patients receiving BBR induction, followed by ASCT and maintenance therapy.

In our study, VRD as induction therapy represents a reduced number of patients. This is consistent with the lack of regulatory approval of novel drugs like bortezomib and lenalidomide in Latin America during the years of recruitment.

In our transplant-eligible cohort, we found that the use of high-dose melphalan (HDM) followed by ASCT achieved a 5-year OS of 60.3%, and a 5-year PFS of 28.1%. However, the heterogeneity in the definition of high-risk cytogenetic alterations between our study and published clinical trials such as EMN02/HO95 and IFM2009 does not allow us to establish a direct comparison of our results and the trials mentioned above.

In the EMN02/HO95 trial, which included VCD as induction therapy, in patients with a high-risk cytogenetic MM even when the use of ASCT improved the OS (HR 0.66; 95%CI 0.45-0.99; p=0.042), but no PFS (HR 0.59; 95%CI 0.34-1.03; p=0.062), the consolidation with double ASCT achieved a higher median PFS of 46.0 months versus 26.7 months with single ASCT, and the 5-year OS in the high-risk cytogenetic subgroup was 61.3% using double ASCT versus 54.7% with single HSCT (HR 0.70, 0.35–1.42; p=0.32).[13]

In the IFM2009 trial, the high-risk cytogenetic did not affect the benefit achieved in patients receiving VRd as induction therapy, HDM with ASCT as consolidative therapy, and lenalidomide maintenance.[24]

High-dose melphalan and ASCT remain as the standard therapy for transplant-eligible patients with MM. Some authors recommend double HDT/ASCT for high-risk NDMM, based on a meta-analysis of 4 randomized European trials which showed that bortezomib therapy plus double ASCT partially improved progression-free survival in patients carrying t(4;14) and del 17p.[25,26] In our study, no patient received double ASCT. In the last 5 years, double ASCT has been included as a reimbursed strategy for high-risk patients in some LATAM countries. However, these are not included in the period of this analysis.

Our study has several limitations, which are associated with the retrospective nature of the registry-based analysis, including the possible heterogeneity in response assessment and treatment choices among the participating centers and countries. Also, the number of patients included is low, which limits the strength of our conclusions. Additionally, the reasons why 40% of ASCT-eligible patients were not transplanted have not been addressed in this study. In a region where ASCT is widely available while novel drugs are not, further research is needed to assess the reasons for this low rate of ASCT. In spite of these limitations, our work has the value of reporting current data, not previously published, from our region.

Conclusions

Although the number of patients is limited, Bortezomib-based induction, ASCT, and maintenance therapy are associated with improved OS in high-risk NDMM patients.

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